

# Neurochemistry immune systems interaction in depression

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## Summary

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Depression is a psychiatric disorder in which all neurotransmitters, endocrine and immune systems are involved. Moreover, these changes can lead to structural changes in the brain. There are different antidepressants developed since mid 20<sup>th</sup> Century and those improved the clinical symptoms though there are still deficiencies. Recently, immune system changes become of interest in pathophysiology of depression and development of new antidepressant. This thesis addressed the role of neuro-immune balance in clinical and experimental depression, and the role of certain current antidepressants and immunomodulation in this context.

Chapter 1.1, the general discussion is the introduction in which the scientific background in brief related to the reason why the hypothesis was formulated.

Chapter 1.2 is the hypothesis formulated upon which this whole thesis was based and the research studies were designed and carried out. This hypothesis explained the integrated role of neuro-immune-endocrine-metabolism interaction in pathophysiology of depression and the possible coping mechanisms.

Chapter 2 addressed the importance of the balance between representative Th1, Th2 and Th3 cytokines in drug naïve or drug free depressed patients and the effect of antidepressant treatment. The results clearly demonstrate that there is an increase in Th1 cytokines and a decrease in Th2 cytokines in depressed and Th3 cytokine increases in patients that recovered from depression.

Chapter 3 addressed the issue that the proinflammatory cytokine IFN $\alpha$  induced depressive-like behaviour in rats and both peripheral and central cytokine changes. The central cytokine changes occurred in the area like hypothalamus and hippocampus, which are involved in depression. Moreover this chapter addressed the preventive role of SSRI paroxetine in IFN $\alpha$ -induced depression.

Chapter 4 addressed the observation that the proinflammatory cytokine, IFN $\alpha$ , induced not only the cytokine changes in the brain, but also reduction in astrocyte density in hippocampus area of the brain in the rats. In addition, this chapter explained that the SSRI antidepressant, fluoxetine could not fully prevent the changes. As the astrocytes play an important role in neuroprotection it seems probable that such irreversible changes could be a prelude to neurodegeneration.

Chapter 5 addressed the fact that immunomodulation could improve the symptoms of depression through an experimental study undertaken in olfactory bulbectomised (OBX) rats which were treated with the cyclooxygenase (COX) 2 inhibitor celecoxib. It was shown that OBX rats treated with celecoxib did not show central pro-inflammatory cytokine changes or the behavioural changes that occurred in the untreated OBX rats.

Chapter 6 addressed the changes in tryptophan and kynurenine pathway metabolites in patients with major depression which demonstrated indirectly that impaired neuroprotection occurred in depressed patients. An imbalance in the neuroprotection-

neurodegeneration kynurenine pathway was indicated by low plasma neuroprotective metabolite, kynurenic acid in depressed patients compared to their healthy controls. Moreover, antidepressant treatment did not reverse this impairment in neuroprotection in those patients with repeated episodes of depression despite the improvement in the clinical symptoms. This finding supports the hypothesis that explains how the cytokine imbalance is related to tryptophan and kynurenine metabolism and how that could lead to impaired neuroprotection in chronic major depression.

In the chapter 7 reviewed the possible relationship between depression and dementia through the metabolic changes that lead to impaired neuroprotection in combination with other associated central inflammatory changes also require evaluation in order to verify the pathophysiological link between depression and dementia.

The last chapter, Chapter 8 discussed on the overall finding through the work in this thesis and the future perspectives.